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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,087	11/20/2001	Stephen G. Sligar	87-00	1280

23713 7590 05/09/2005

GREENLEE WINNER AND SULLIVAN P C
4875 PEARL EAST CIRCLE
SUITE 200
BOULDER, CO 80301

EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,087	SLIGAR ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,41-49 and 52-59* is/are pending in the application.

4a) Of the above claim(s) *44-49 and 52-58* is/are withdrawn from consideration.

5)☒ Claim(s) *59* is/are allowed.

6)☒ Claim(s) *37 and 41* is/are rejected.

7)☒ Claim(s) *42 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

Applicants' amendment filed on 02/17/2005 has been entered. Claims 37, 41, 43, 49, 52, and 59 have been amended. Claims 37, 41-49 and 52-59 are pending. Claims 37, 41-43, and 59 are under consideration.

It is noted that examination has been extended to additional artificial tandem repeat variant sequences, which are recited in the Markush group of claims 42 and 59.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Withdrawn Objections and/or Rejections

The rejection of claims 37, 42, and 43 under 35 U.S.C. 112, first paragraph for scope of enablement, as set forth at pages 3-5 of the previous Office Action (Paper No. 12272004, mailed on 12/30/2004), has been withdrawn in view of amended claim 37.

The rejection of claims 37 and 39-43 under 35 U.S.C. 112, second paragraph as set forth at page 5 of the previous Office Action (Paper No. 12272004, mailed on

12/30/2004), has been withdrawn in view of the amended claim 37 and canceled claims 39 and 40.

The rejection of claims 39 and 40 under 35 U.S.C. 103(a) as being unpatentable over Bayburt et al. (*Journal of Structural Biology* 123:37-44, 1998) in view of Barnes et al. (Neuropharmacology 38:1083-1152, 1999) has been made moot by the canceled claims.

The objection to claims 42 and 59 for reciting non-elected subject matter—amino acid sequences (SEQ ID NOS: 6, 9, 19, 23, 29, 43-45)—has been withdrawn in view of Applicants' argument that these sequences are artificial tandem repeat variant sequences, which are cited in a proper Markush group and share a common structural characteristics.

Claim Rejections under 35 USC § 103 (a)

The rejection of claims 37 and 41 under 35 U.S.C. 103(a) as being unpatentable over Bayburt et al. (*Journal of Structural Biology* 123:37-44, 1998) in view of Barnes et al. (Neuropharmacology 38:1083-1152, 1999), as set forth in Paper No. 12272004 (mailed on 12/30/2004), is maintained.

Beginning at the bottom of page 8 of Applicants' response filed on 02/17/2005, Applicants argue that the present claims encompass artificial membrane scaffold

proteins neither taught nor suggested by the cited Bayburt reference. Applicants argue that the Bayburt paper describes particles prepared using cytochrome reductase and naturally occurring human apolipoprotein A-1. Applicants submit that the specification gives numerous non-limiting examples of the kinds of differences in structure between natural apo A-1 and thus the artificial membrane scaffold proteins of the present invention are clearly distinguished in structure from naturally occurring human proteins.

Applicants' argument has been fully considered, but is not deemed to be persuasive because the term "artificial" does not limit the scope of the claimed invention and does not distinguish the scaffold protein recited in the instant claims from those taught in the art because a membrane scaffold protein, e.g., apo A-I protein, can be made by DNA recombinant technology and such an artificial scaffold protein can have the same sequence as that of a membrane scaffold protein isolated from a natural source. The specification does not provide an unambiguous definition for the term "artificial" that clearly excludes those membrane scaffold proteins that have the same structure as that of naturally occurring membrane scaffold proteins

Beginning at the bottom of page 9 of Applicants' response filed on 02/17/2005, Applicants argue that the reference of Bayburt et al. teaches cytochrome P450 reductase, a tethered membrane protein, not an integral membrane protein. Referring to the definition, Applicants submit that tethered membrane proteins have single pass

membrane proteins and GPCRs, identified in the present application as integral membrane proteins, have seven transmembrane domains.

Applicants' argument has been fully considered, but is not deemed to be persuasive because Bayburt et al. clearly teach NADPH-cytochrome P450 reductase is an integral membrane protein (2nd paragraph of left column of page 38). NADPH-cytochrome P450 reductase is also recognized as an integral membrane protein in additional references (e.g., Bayburt et al., *Langmuir*, 16: 5993-5997, June 17, 2000).

At the bottom of page 10 of Applicants' response filed on 02/17/2005, Applicants argue that there is nothing in either of the cited references that either suggested the combination of artificial membrane scaffold protein and GPCR as currently claimed, and there is nothing in the references that provides any reasonable expectation of success for combining a protein with such complex interaction with a lipid bilayer so that the functional properties of the protein would be maintained.

Applicants' argument has been fully considered, but is not deemed to be persuasive because it would have been obvious to one having ordinary skill in the art at the time the invention was made to reconstitute a GPCR, such as a 5-hydroxytryptamine receptor in the nanometer-size phospholipid bilayer taught by Bayburt et al. with a reasonable expectation of success. One would have been motivated to do so because Bayburt et al. clearly demonstrate the success of reconstitution and imaging of an

integral membrane protein, NADPH-cytochrome P450 reductase in a nanometer-size phospholipid bilayer and teach that this can be used as a novel approach for the study of mechanical and functional properties of single-membrane proteins in a bilayer environment, which represents a physiologically relevant condition and because Barnes et al. teach that pharmacological manipulation of the central 5-hydroxytryptamine system has therapeutically potential. Moreover, the demonstration of the success of reconstitution of an active integral membrane protein, NADPH-cytochrome P450 reductase, which is a complex membrane protein enzyme system, in a nanometer-size phospholipid bilayer illustrates the reasonable expectation of success that one of skilled in the art reconstitute other membrane proteins, such as 5-hydroxytryptamine receptor, a GPCR.

At the top of page 11 of Applicants' response filed on 02/17/2005, Applicants argue that the reference of Barnes et al. does nothing to remedy the failure of Bayburt to teach or suggest structural alteration of the MSP. This is not found to be persuasive because the reference of Bayburt et al. teaches the membrane scaffold protein recited in the instant claims, as noted above. The reference of Barnes et al. is cited to provide a motivation for one skilled in the art to reconstitute a 5-hydroxytryptamine receptor in the nanometer-size phospholipid bilayer taught by Bayburt et al.

At the 2nd paragraph of page 11 of Applicants' response filed on 02/17/2005, Applicants argue that there is nothing in the cited Barnes reference which would motivate one of

ordinary skill in the art to combine a 5-hydroxytryptamine receptor with naturally occurring apolipoprotein a-1 or with any artificial membrane scaffold protein as taught in the specification. Citing case law, applicants submit that the court have cautioned against the impermissible use of hindsight in evaluating patentability.

Applicants' argument has been fully considered, but is not deemed to be persuasive because, in combination with the teaching of Bayburt et al that reconstitution of an integral membrane protein, NADPH-cytochrome P450 reductase in a nanometer-size phospholipid bilayer can be used for studying mechanical and functional properties of single-membrane proteins in a physiologically relevant condition, the teaching of Barnes et al. provides a motivation to reconstitute a GPCR, such as 5-hydroxytryptamine in a nanometer-size phospholipid bilayer because there is a high level of interest in the actions of 5-hydroxytryptamine and pharmacological manipulation of the central 5-hydroxytryptamine system has therapeutically potential.

Regarding Applicants argument about the impermissible use of hindsight, the Examiner notes that it is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art *In re Keller,* 642 F.2d 413, 288 USPQ 871 9ccpa 1981).

Claim Objection

Claims 42 and 43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claim 59 is allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (571) 272-0829. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

Ruixiang Li

Ruixiang Li, Ph.D.
Examiner
May 4, 2005